# PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

CORRECTED VERSION

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Corrected version!

| Applicant's or agent's file reference PCT-197 | **FOR FURTHER ACTION** See Form PCT/IPEA/416 | |
|---|---|---|
| International application No. PCT/ES2004/000549 | International filing date *(day/month/year)* 09.12.2004 | Priority date *(day/month/year)* 09.12.2003 |
| International Patent Classification (IPC) or national classification and IPC INV. A61P27/02 | | |
| Applicant UNIVERSIDAD MIGUEL HERNANDEZ et al. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 29.07.2005 | 24.04.2006 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Fayos, C Telephone No. +49 89 2399-2180 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/ES2004/000549

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   **Description, Pages**

   1-16 as originally filed

   **Claims, Numbers**

   1-25 received on 29.03.2006 with letter of 29.03.2006

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1-25
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15-25 (industrial applicability)

because:

☒ the said international application, or the said claims Nos. 15-25 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 4-11, 18-25 |
| | No: | Claims | 1-3, 12-17 |
| Inventive step (IS) | Yes: | Claims | 5-11, 18-25 |
| | No: | Claims | 1-4, 12-17 |
| Industrial applicability (IA) | Yes: | Claims | 1-14; 15-25 see separate sheet |
| | No: | Claims | - |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

All applicant's arguments in the letter dated 29.03.2006 have been taken into consideration.

**Comments on item I**

1- With the letter dated 29.03.2006, new claims 1-25 have been filed which introduce subject matter which goes beyond the contents of the originally filed application, contrary to Art. 34 PCT.

The amendments concern the exclusion of neurotrophic factor stimulators in claims 1, 12, 15, which has no basis in the originally filed application.

The disclaimer formulated on the basis of a certain disclosure (here D1) is not allowable since D1 is of relevance for further examination of the claimed invention and it part of the prior art field to be taken into consideration. D1 undisputedly relates to the same field as that of the claimed invention, therefore, the disclaimer can not be allowed because the subject-matter to be disclaimed is considered relevant to the assessment of inventive step.

Therefore, the IPER is based on the originally filed version of the claims only.

**Comments on item III**

2- Claims 15-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Comments on item V**

3- The documents cited in the International Search Report correspond respectively to D1-D4. Any reference to the documents in the present written opinion relates to the passages given in said report, unless otherwise indicated.

D1: WO 03 020281 A1
D2: US-A-5 767 079
D3: US-B1-6 350 781

D4: US-A-3 374 144

4- D1 refers to the use of compounds acting on damaged nerve endings for the treatment of dryness of the surface of the human eye caused by photorefractive surgery. It is noted that the expression "blocking agent of the electrical activity of the damaged nerve ending of the neuroma" does not appear to correspond to a group of compounds with a clear meaning for the skilled person (see item VIII below). Since the neurotrophic factor stimulators of D1 exert their action at least partially on voltage-dependent channels, this document discloses subject-matter overlapping with that of present claim 1-3 and 12-17. Furthermore, D3 and D4 disclose ophthalmic lidocaine compositions which anticipate the subject-matter of claims 12-14.

5- The subject-matter of claims 4 and 18 cannot be regarded as inventive, since it seems unlikely that all the embodiments covered provide a solution to the technical problem posed (provision of alternative treatment for dryness of the surface of the human eye caused by photorefractive surgery). Despite the fact that all the families covered in claims 4 and 18 must exert their physiological action throughout blockage of ion channels because of their respective claim dependencies, it would clearly be an undue burden for the skilled man to check all possible compounds belonging to all the families mentioned for their ability to block ion channels. In that sense, an inventive step appears to be lacking for the subject matter of these claims.

6- The subject-matter of claims 5-11 and 18-25 can be regarded as being novel and inventive: none of the available documents relates to or gives a hint about the particular compounds cited for the medical indication specified in claim 1.

7- For the assessment of the present claims 15-25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Comments on item VIII**

8- The term "blocking agent of the electrical activity of the damaged nerve ending of the

neuroma, as a consequence of its blocking action of the ion channel" used in claims 1 and 15 is still vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT. Furthermore, it is noted that sufficiency of disclosure is lacking in the sense of Art. 5 PCT, as the invention as claimed cannot be carried out by a skilled person, without undue burden or without the need of inventive skill in order to determine which agents (compounds) fall within the scope of the claims without any hint towards their structure or chemical identity.

**CLAIMS**

**1.** Use of a blocking agent of the electrical activity of the damaged nerve endings of the neuroma, as a consequence of its blocking action on the ion channels, excluding neurotrophic factor stimulators, particularly selected from: neotrofin, idebenone, CB-1093, (1-(1-butyl)-4-(2-oxo-1-benzimidazolone) piperidine, SS-701, KT-711, ONO-2506 and clenbuterol, for the preparation of a medicinal product for the treatment of dryness of the surface of the human eye caused by photorefractive surgery.

**2.** Use according to claim 1, in which the photorefractive surgery is an excimer laser photorefractive keratectomy or a laser-assisted in situ keratomileusis.

**3.** Use according to any one of the preceding claims, characterized in that the blocking agent is selected from those that exert their action on the voltage-dependent sodium, calcium, chlorine and potassium channels.

**4.** Use according to any one of the preceding claims, characterized in that the blocking agent is selected from the group comprising antiepileptics, anticonvulsants, anti-arrhythmic drugs, tricyclic antidepressants and local anaesthetics, and combinations thereof.

**5.** Use according to claim 4, characterized in that the blocking agent is selected from the group comprising lidocaine, tocainide, n-benzyl analogues of tocainide, mexiletine, lamotrigine, carbamazepine, phenytoin, amitriptyline, N-phenylethyl amitriptyline, desipramine, gabapentin, nifekalant, venlafaxine, nefazodone, pregabalin, and the pharmaceutically acceptable salts thereof.

**6.** Use according to claim 5, characterized in that the blocking agent is carbamazepine.

**7.** Use according to claim 5, characterized in that the blocking agent is phenytoin.

**8.** Use according to claim 5, characterized in that the blocking agent is mexiletine.

**9.** Use according to claim 5, characterized in that the blocking agent is lidocaine.

**10.** Use according to claim 5, characterized in that the blocking agent is tocaidine.

**11.** Use according to claim 5, characterized in that the blocking agent is pregabalin.

**12.** Pharmaceutical composition for ophthalmic application that comprises a therapeutically effective amount of a blocking agent of the electrical activity of the damaged nerve endings of the neuroma, as a consequence of its blocking action on the ion channels, excluding neurotrophic factor stimulators, particularly selected from: neotrofin, idebenone, CB-1093, (1-(1-butyl)-4-(2-oxo-1-benzimidazolone) piperidine, SS-701, KT-711, ONO-2506 and clenbuterol; and also excluding lidocaine, together with suitable amounts of pharmaceutically acceptable excipients for constituting an ophthalmic formulation.

**13.** Composition according to claim 12, characterized in that the blocking agent is in an amount between 0.0005 and 1% (w/v).

**14.** Composition according to claim 13, characterized in that the blocking agent is in an amount between 0.0005 and 0.1% (w/v).

**15.** Method of treatment of a mammal, including a human, suffering from dryness of the ocular surface caused by photorefractive surgery, which comprises the ophthalmic administration of an agent for blocking the electrical activity of the damaged nerve endings of the neuroma, as a consequence of its blocking action on the ion channels, excluding neurotrophic factor stimulators, particularly selected from: neotrofin, idebenone, CB-1093, (1-(1-butyl)-4-(2-oxo-1-benzimidazolone) piperidine, SS-701, KT-711, ONO-2506 and clenbuterol, together with suitable amounts of pharmaceutically acceptable excipients for constituting a topical formulation.

**16.** Method according to claim 15, characterized in that the photorefractive surgery is an excimer laser photorefractive keratectomy or a laser-assisted in situ keratomileusis.

**17.** Method according to any one of the claims 15-16, characterized in that the blocking agent is selected from those that exert their action on the voltage-dependent sodium, calcium, chlorine and potassium channels.

**18.** Method according to any one of the claims 15-17, characterized in that the blocking agent is selected from the group comprising antiepileptics, anticonvulsants, anti-arrhythmic drugs, tricyclic antidepressants and local anaesthetics, and combinations thereof.

**19.** Method according to claim 18, characterized in that the blocking agent is selected from the group comprising lidocaine, tocainide, n-benzyl analogues of tocainide, mexiletine, lamotrigine, carbamazepine, phenytoin, amitriptyline, N-phenylethyl amitriptyline, desipramine, gabapentin, nifekalant, venlafaxine,

nefazodone, pregabalin, and the pharmaceutically acceptable salts thereof.

**20.** Method according to claim 19, characterized in that the blocking agent is carbamazepine.

**21.** Method according to claim 19, characterized in that the blocking agent is phenytoin.

**22.** Method according to claim 19, characterized in that the blocking agent is mexiletine.

**23.** Method according to claim 19, characterized in that the blocking agent is lidocaine.

**24.** Method according to claim 19, characterized in that the blocking agent is tocaidine.

**25.** Method according to claim 19, characterized in that the blocking agent is pregabalin.